

EXHIBIT 1

IN THE CLAIMS

Please cancel claims 1-58 and add new claims 59-120.

- 59. (New) A first generation recombinant adenovirus vector comprising:
- A left adenovirus inverted terminal repeat sequence;
 - An adenoviral packaging sequence 3' to the left adenovirus inverted terminal repeat sequence;
 - A first inverted repeat sequence 3' to the adenovirus packaging sequence;
 - A transgene cassette sequence 3' to the first inverted repeat sequence;
 - A second inverted repeat sequence as in (c) 3' to the transgene cassette;
 - At least one adenoviral sequence which directs adenoviral replication 3' to the right inverted repeat; and
 - A right adenoviral inverted terminal repeat sequence 3' to the adenoviral replication gene.
- 60. (New) The adenovirus vector of claim 59, wherein the left and right adenovirus inverted terminal repeat sequences and the packaging sequence are from the same adenoviral serotype.
- 61. (New) The adenovirus vector of claim 59, wherein the first inverted repeat sequence is a left inverted terminal repeat sequence and the second inverted repeat sequence is a right inverted terminal repeat sequence.

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- 62. (New) The adenovirus vector of claim 59, wherein the first inverted repeat sequence comprises an adenoviral-associated left inverted terminal repeat sequence and the second inverted repeat sequence comprises an adenoviral-associated right inverted terminal repeat sequence.
- 63. (New) The adenovirus vector of claim 59, wherein the sequence which directs adenoviral tropism comprises a sequence on the anti-parallel strand which encodes an adenoviral fiber protein including a fiber tail, a fiber shaft, and a fiber knob, wherein the fiber knob includes a G-H loop region.
- 64. (New) The adenovirus vector of claim 63, wherein the sequence on the anti-sense strand which encodes the fiber tail is from the same serotype as the adenoviral inverted repeat sequence.
- 65. (New) The adenovirus vector of claim 59, wherein the transgene cassette sequence comprises a 5' portion of a gene of interest.
- 66. (New) The adenovirus vector of claim 59, wherein the transgene cassette sequence comprises a 3' portion of a gene of interest.
- 67. (New) The adenovirus vector of claim 59, wherein the transgene cassette sequence comprises:
- a) A polyadenylation sequence;
 - b) A transgene sequence 3' to the polyadenylation sequence; and
 - c) A promoter sequence 3' to the transgene sequence.
- 68. (New) The adenovirus vector of claim 59, wherein the transgene cassette sequence comprises:
- a) A promoter sequence;

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- b) A transgene sequence 3' to the promoter sequence; and
- c) A polyadenylation sequence 3' to the transgene sequence.

--69. (New) The adenovirus vector of claim 67 or 68, wherein the transgene sequence is selected from a group consisting of a therapeutic gene, a selectable gene, and a reporter gene.

--70. (New) The adenovirus vector of claim 69, wherein the therapeutic gene is selected from a group consisting of gamma globin, and human alpha-1 anti-trypsin.

--71. (New) The adenovirus vector of claim 69, wherein the selectable gene is selected from a group consisting of neomycin, ampicillin, penicillin, tetracycline, and gentamycin.

--72. (New) The adenovirus vector of claim 69, wherein the reporter gene is selected from a group consisting of green fluorescent protein, beta galactosidase, alkaline phosphatase.

--73. (New) The transgene cassette of claim 67 or 68, further comprising an insulator element.

--74. (New) The transgene cassette of claim 67 or 68, further comprising a bacterial origin of replication.

--75. (New) The adenoviral vector of claim 59, wherein the adenoviral sequences which direct adenoviral replication are selected from a group consisting of E2 and E4; E1, E2 and E4; E2 and E4; and E2, E3, and E4.

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--76. (New) A first generation recombinant adenovirus vector which targets a host cell of interest and a portion of which integrates into the host cell genome so targeted, comprising two DNA strands, each strand being antiparallel to the other, the first strand comprising:

- a) A left adenovirus inverted terminal repeat sequence;
- b) An adenoviral packaging sequence 3' to the left adenovirus inverted terminal repeat sequence;
- c) A first inverted repeat sequence 3' to the adenoviral packaging sequence;
- d) A transgene cassette sequence 3' to the adenoviral packaging sequence;
- e) A second inverted repeat sequence 3' to the transgene cassette;
- f) At least one adenoviral sequence which directs adenoviral replication 3' to the second inverted repeat sequence; and
- g) A right adenoviral inverted terminal repeat sequence 3' to the adenoviral sequence which directs replication, wherein the left and right terminal repeat sequences permit integration of the transgene cassette sequence into the host cell genome, and wherein the second strand comprises a sequence which encodes an adenoviral fiber protein that permits targeting of the vector into the host cell of interest.

--77. (New) The adenovirus vector of claim 76, wherein the adenoviral protein includes a fiber tail, a fiber shaft, and a fiber knob, wherein the fiber knob includes a G-H loop region.

--78. (New) The adenovirus vector of claim 76, wherein the left and right adenovirus inverted terminal repeat sequences and the packaging sequence are from the same adenoviral serotype.

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- 79. (New) The adenovirus vector of claim 77, wherein the fiber tail is from the same serotype as the left and right adenoviral inverted repeat sequences.
- 80. (New) The adenovirus vector of claim 77, wherein the fiber shaft is from a different serotype as the left and right adenoviral inverted repeat sequences.
- 81. (New) The adenovirus vector of claim 80, wherein the fiber shaft is from a serotype selected from a group consisting of serotype 3, 7, 9, 11, and 35.
- 82. (New) The adenovirus vector of claim 77, wherein the fiber shaft comprises a shortened length.
- 83. (New) The adenovirus vector of claim 77, wherein the fiber knob is from a different serotype as the left and right adenoviral inverted repeat sequences.
- 84. (New) The adenovirus vector of claim 83, wherein the fiber knob is from a serotype selected from a group consisting of serotype 3, 7, 9, 11, and 35.
- 85. (New) The adenovirus vector of claim 77, wherein the fiber knob is a modified fiber knob protein comprising the G-H loop replaced with a heterologous peptide ligand sequence which binds to at least one surface protein on the host cell of interest.
- 86. (New) The adenovirus vector of 76, wherein the first inverted repeat sequence is a left inverted terminal repeat sequence and the second inverted repeat sequence is a right inverted terminal repeat sequence.

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- 87. (New) The adenovirus vector of 76, wherein the first inverted repeat sequence comprises an adenoviral-associated left inverted terminal repeat sequence and the second inverted repeat sequence comprises an adenoviral-associated right inverted terminal repeat sequence.
- 88. (New) The adenovirus vector of claim 76, wherein the transgene cassette sequence comprises:
- a) A polyadenylation sequence;
 - b) A transgene sequence 3' to the polyadenylation sequence; and
 - c) A promoter sequence 3' to the polyadenylation sequence.
- 89. (New) The adenovirus vector of claim 76, wherein the transgene cassette sequence comprises:
- a) A promoter sequence;
 - b) A transgene sequence 3' to the promoter sequence; and
 - c) A polyadenylation sequence.
- 90. (New) The adenovirus vector of claim 88 or 89, wherein the transgene sequence is selected from a group consisting of a therapeutic gene, a selectable gene, and a reporter gene.
- 91. (New) The adenovirus vector of claim 90, wherein the therapeutic gene is selected from a group consisting of gamma globin, and human alpha-1 anti-trypsin.
- 92. (New) The adenovirus vector of claim 90, wherein the selectable gene is selected from a group consisting of neomycin, ampicillin, penicillin, tetracycline, and gentamycin.

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- 93. (New) The adenovirus vector of claim 90, wherein the reporter gene is selected from a group consisting of green fluorescent protein, beta galactosidase, alkaline phosphatase.
- 94. (New) The transgene cassette of claim 88 or 89 further comprising an inverted repeat sequence located 3' to the left inverted terminal repeat sequence or located 5' to the right inverted terminal repeat sequence.
- 95. (New) The transgene cassette of claim 88 or 89, further comprising an insulator element.
- 96. (New) The transgene cassette of claim 88 or 89, further comprising a bacterial origin of replication.
- 97. (New) The adenoviral vector of claim 76, wherein the adenoviral sequences which direct adenoviral replication are selected from a group consisting of E2 and E4; E1, E2 and E4; E2 and E4; and E2, E3, and E4.
- 98. (New) A recombinant gutless adenovirus vector a portion of which integrates into a host cell genome, comprising:
- a) A left adenovirus inverted terminal repeat sequence;
 - b) An first adenoviral packaging sequence 3' to the left adenovirus inverted terminal repeat sequence;
 - c) A first inverted repeat sequence 3' to the adenoviral packaging sequence;
 - d) A transgene cassette sequence 3' to the first inverted repeat sequence;
 - e) A second inverted repeat sequence 3' to the transgene cassette; and
 - f) An second adenoviral packaging sequence 3' to the second inverted repeat sequence; and

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g) A right adenoviral inverted terminal repeat sequence 3' to the second adenoviral packaging sequence, wherein the left and right terminal repeat sequences permit integration of the transgene cassette sequence into the host cell genome.

--99. (New) The adenovirus vector of claim 98, wherein the left and right adenovirus inverted repeat sequences and the packaging sequences are from the same adenoviral serotype.

--100. (New) The adenovirus vector of claim 98, wherein the transgene cassette sequence comprises:

- a) A polyadenylation sequence;
- b) A transgene sequence 3' to the polyadenylation sequence; and
- c) A promoter sequence 3' to the polyadenylation sequence.

--101. (New) The adenovirus vector of claim 98, wherein the transgene cassette sequence comprises:

- a) A promoter sequence;
- b) A transgene sequence 3' to the promoter sequence; and
- c) A polyadenylation sequence 3' to the transgene cassette.

--102. (New) The adenovirus vector of claim 98, wherein the first inverted repeat sequence is a left inverted terminal repeat sequence and the second inverted repeat sequence is a right inverted terminal repeat sequence.

--103. (New) The adenovirus vector of claim 98, wherein the first inverted repeat sequence comprises an adenoviral-associated left inverted terminal repeat sequence and the second inverted repeat sequence comprises an adenoviral-associated right inverted terminal repeat sequence.

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- 104. (New) The adenovirus vector of claims 100 or 101, wherein the transgene sequence is selected from a group consisting of a therapeutic gene, a selectable gene, and a reporter gene.
- 105. (New) The adenovirus vector of claim 104, wherein the therapeutic gene is selected from a group consisting of gamma globin, and human alpha-1 anti-trypsin.
- 106. (New) The adenovirus vector of claim 104, wherein the selectable gene is selected from a group consisting of neomycin, ampicillin, penicillin, tetracycline, and gentomycin.
- 107. (New) The adenovirus vector of claim 104, wherein the reporter gene is selected from a group consisting of green fluorescent protein, beta galactosidase, alkaline phosphatase.
- 108. (New) The adenovirus vector of claim 100 or 101, further comprising an insulator element.
- 109. (New) The adenovirus vector of claim 100 or 101, further comprising a bacterial origin of replication.
- 110. (New) A method of producing a resolved gutless adenovirus vector in a suitable cell, said method comprising introducing a first and a second adenovirus vector genome of claim 59 or 76 into the cell under suitable conditions so that the recombinant adenovirus vectors undergo homologous recombination thereby producing a resolved gutless adenovirus vector.

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- 111. (New) A resolved gutless adenovirus vector produced by the method of claim 110.
- 112. (New) The method of claim 110, wherein the first adenovirus vector comprises a transgene cassette having a 5' portion of a gene of interest, and wherein the second adenovirus vector comprises a transgene cassette having a 3' portion of the gene of interest, and wherein a part of the 5' portion overlaps with a part of the 3' portion so that homologous recombination occurs.
- 113. (New) A method of producing a resolved gutless recombinant Ad vector by homologous recombination in a suitable cell, said method comprising contacting two parental recombinant Ad vectors, each comprising a transgene cassette containing a portion of a selected transgene with a region of overlapping homology, so that the first and second parental recombinant Ad vectors undergo homologous recombination at the region of overlapping homology, resulting in a resolved recombinant gutless Ad vector having both portions of the selected transgene, and wherein the selected transgene is within a transgene cassette flanked by a pair of ITRs.
- 114. (New) A resolved gutless adenovirus vector produced by the method of claim 113.
- 115. (New) An adenovirus library comprising a plurality of adenovirus vectors from claim 59, 76 or 98 expressing fiber proteins which are displayed and modified by random peptide insertions.
- 116. (New) The library of claim 115, wherein said fiber protein so displayed comprises a random peptide substituted in the G-H loop of the fiber protein knob domain.

- 117. (New) A screening method for targeting adenovirus vectors for gene therapy comprising contacting the adenovirus library of claim 115 with a plurality of cells so that the cells are transduced with the adenovirus vectors of the adenovirus library transduction occurs and detecting the cells so transduced.
- 118. (New) The adenovirus vector of claim 67, 68, 88, 89, 100, or 101 further comprising a nucleotide sequence encoding a rep78 protein.
- 119. (New) The adenovirus vector of claim 61, 86, and 102, wherein the inverted terminal repeat sequences are from the same adenovirus serotype.
- 120. (New) The adenovirus of claim 100 or 101 further comprising an inverted repeat sequence located 3' to the left inverted terminal repeat sequence or located 5' to the right inverted terminal repeat sequence.

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